



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,407	10/12/1999	TERRY L. DELOVITCH	087300-00040	5078

20350 7590 08/27/2002

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

ROARK, JESSICA H

ART UNIT	PAPER NUMBER
----------	--------------

1644

DATE MAILED: 08/27/2002

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/341,407

Applicant(s)

DELOVITCH, TERRY L.

Examiner

Jessica H. Roark

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8 and 9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 October 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

Art Unit: 1644

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/5/02 (Paper No. 17), is acknowledged.
Claims 7 and 10-31 have been cancelled.
Claims 1, 2 and 9 have been amended.
Claims 1-6 and 8-9 are pending and are under consideration in the instant application.
2. In order to facilitate the prosecution of this application, Applicant is again requested to cancel all non-elected embodiments from the claims.
3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. This Office Action will be in response to applicant's arguments, filed 6/5/02 (Paper No. 17). The rejections of record can be found in a previous Office Action (Paper Nos. 10 and 15).
4. Applicant's comment regarding allowable subject matter in view of the omission of claim 9 from the heading of any rejection of record in Paper No.15 is acknowledged. While claim 9 was clearly addressed in the body of the rejection under 35 USC 103(a) in Paper No. 15, the instant Office Action will include New Grounds of Rejection.
5. Claims 1-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing the development of autoimmune diabetes in a pre-diabetic subject identified as susceptible to the development of diabetes by administering an agonist antibody to CD28; does not reasonably provide enablement for a method of preventing the development of other autoimmune diseases (claims 1-6), preventing the development of diabetes in individuals not susceptible to the development of diabetes (claims 8-9), or a method employing any "CD28 agonist" (claim 1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
Applicant's arguments, filed 6/5/02, with respect to the rejections of record have been fully considered, but have not been found convincing.

Art Unit: 1644

With respect to the rejection of record in Paper Nos. 10 and 15 as to the scope of diseases which can be prevented by administering a CD28 agonist, Applicant again argues that a method which results in the stimulation of a TH2 type of T cell response is broadly applicable to a number of autoimmune diseases, irrespective of the antigens involved. Applicant also emphatically disagrees that literature regarding the unpredictable effect of antagonizing B7-1 and/or B7-2 (the ligands of CD28) can serve as a basis for concluding that the effect of activating CD28 in various disease models is unpredictable. Applicant further argues that autoantibodies in general provide prognostic indicators and guides to the appropriate timing of therapeutic intervention, relying upon the previously discussed use of anti-GAD autoantibodies for development of autoimmune diabetes. Finally, Applicant asserts that the specification enables one skilled in the art to identify other CD28 agonists, using the assays methods described in the specification.

The Examiner has previously pointed to the review by Thompson (Cell 1995; 81:979-982, IDS# AO) as evidence that the skilled artisan recognized the complexities associated with the B7-1/B7-2/CD28 signaling pathways in various autoimmune diseases (see Paper Nos. 10 and 15). The Examiner notes that the skilled artisan recognized that studies blocking one or both of the ligands of CD28 do speak to requirements for CD28 signaling, since blocking one of B7-1 or B7-2 alters that timing and duration of CD28 stimulation; and that studies blocking both B7-1 and B7-2 provide insight into the effects of antagonizing CD28 signaling. While these studies do not directly assess the effect of agonizing CD28 signaling, they nevertheless do clearly indicate the complexity of the system and the unpredictable nature of generalizing results obtained in any one autoimmune disease to other autoimmune diseases.

Further, as previously noted in Paper No. 15, not all autoimmune diseases would be viewed by the skilled artisan as likely to benefit from stimulating a TH2 type of immune response (i.e., inhibiting a TH1 type of response). The Examiner again notes that many autoimmune diseases, particularly systemic autoimmune diseases such as lupus (specifically recited in instant claim 2), are generally considered to be the *result* of a TH2 type of response. In such autoimmune diseases the skilled artisan would expect that antagonists, rather than agonists, of signaling via CD28 would be more beneficial. Consistent with this, Liang et al. (J. Immunol. 1999; 163:2322-2329, of record) teach that amelioration of lupus is brought about by treatments that block both B7 molecules (see entire document, especially Discussion on page 2328). Blocking both B7 molecules would be expected to antagonize CD28 signaling since neither B7-2 nor B7-1 would be available to stimulate CD28 on T cells.

In addition, the Examiner again notes that while several autoimmune diseases can be broadly characterized as "TH1 type" based upon cytokine profiles and cellular immunity (such as the experimental allergic neuritis model of Ekerfelt et al. (IDS #2) and the autoimmune uveoretinitis model of Saoudi et al. (IDS #4) cited by Applicant); these disease are nevertheless diverse. The skilled artisan recognized that different antigens are involved in these different diseases and that the timing of antigen exposure differs for each antigen and therefore the timing for interventional therapy also differs.

The TH1 diseases discussed by Saoudi et al. and Ekerfelt et al. *are experimentally induced*, so the timing of antigen stimulation is known, thus intervention to prevent the development of the immune response is possible. This is not usually the case in human autoimmune diseases which arise spontaneously. The pathophysiology and natural history of different autoimmune diseases is distinct. Thus the ability to identify susceptible individuals varies greatly for each disease and depends upon disease-specific criteria; consequently the ability to intervene at a particular point in the development of the immune response (a pre-requisite for "preventing" the development of a disease) varies greatly. However, the skilled artisan recognized that such intervention was not possible for most other spontaneous autoimmune diseases. Applicant does not appear to provide sufficient guidance in the specification as to how the skilled artisan may identify at-risk individual for other autoimmune diseases. Without such guidance, enablement is not commensurate in scope with the instant claims.

Art Unit: 1644

The Examiner therefore maintains that given the complexities recognized in the art with respect to modulation of CD28 signaling in various autoimmune diseases and the limited guidance with respect to preventing autoimmune diseases other than autoimmune diabetes (IDDM) provided by the specification as filed; it would require undue experimentation of the skilled artisan to practice the instant methods as broadly claimed for any number of autoimmune diseases associated with increased TH1 immune cell activity (claims 1 and 3-6), or even for the diseases recited in instant claim 2.

In addition, although the Examiner has previously acknowledged in Paper No. 15 that anti-GAD autoantibodies and a clear HLA association may permit the skilled artisan to identify individuals at risk of developing autoimmune diabetes, and therefore provide an opportunity to intervene in at risk individuals to prevent later development of the disease; after further consideration of the claim language it is noted that no claim requires that the method be carried out in an individual susceptible to the development of diabetes. In order to be preventive, any treatment clearly must be initiated before immune destruction of the islets begins. In addition, guidance is required as to those subjects to be treated and those to be left untreated. The instant claims are not limited either to "pre-diabetics", or those susceptible to development of diabetes. Since autoimmune diabetes was recognized by the state of the art not to be preventable once a subject was overtly diabetic; upon further consideration it appears that undue experimentation would also be required of the skilled artisan to practice the instant method, even were the autoimmune disease associated with increased TH1 immune cell activity limited to autoimmune diabetes (claim 8) or initiated in a human subject aged from about 6 months to about 2-3 years (claim 9).

In addition, the Examiner once again notes that although the specification provides a working example of an agonist CD28 antibody, and provides guidance as to how to identify forms of a B7-2 protein with CD28 agonist activity for use in the instant method (e.g. specification at page 7, lines 19-34); there does not appear to be sufficient guidance with respect to how to make and use other "CD28 agonists" commensurate in scope with instant claim 1.

While "CD28 agonist" may have some notion of a desired activity; there is insufficient biochemical or structural information to enable the skilled artisan to make and use the "CD28 agonist", as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). Instant claim 1 as currently recited still encompasses *any* molecule with the function of a "CD28 agonist"; thus for instant claim 1, enablement does not appear to be commensurate with the scope of the claim.

In view of the complex nature of the CD28/B7 pathway and the lack of predictability associated with manipulating this pathway in autoimmune diseases other than diabetes and in individuals other than those both pre-diabetic and susceptible to development of diabetes, and with CD28 agonists other than CD28 agonist antibodies or CD28 agonist forms of B7-2; the limited working example of only a method of administering anti-CD28 agonist antibodies to pre-diabetic animals susceptible of developing diabetes; and the lack of guidance with respect to diseases other than diabetes, subject populations, or other CD28 agonists; the skilled artisan would not be able to practice the invention commensurate in scope with the instant claims, without undue experimentation.

Art Unit: 1644

6. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant asserts in the response filed 6/5/02 that a person of ordinary skill in the art can recognize whether or not a molecule is a CD28 agonist based on the teachings of the specification.

However, as previously noted, while agonists comprising antibodies to CD28 and forms of B7-2 proteins having CD28 agonist activity do appear to have adequate written support in the specification as filed; these two species are structurally diverse. "CD28 agonist" is a broad genus *encompassing any molecule with that activity*. However, only two species with this activity appear to be disclosed and this is insufficient to support a genus encompassing structurally diverse molecules ranging from antibodies to peptidomimetics to inorganic compounds. Nor does Applicant appear to identify a relevant identifying characteristic that would permit the skilled artisan to recognize which molecules were included in the genus. Thus there is insufficient written description in the specification as-filed of a "CD28 agonist" as recited in the claims.

The Examiner again notes that the claimed invention may be adequately described if there is a (1) sufficient description of a *representative number of species*, or (2) by disclosure of *relevant, identifying characteristics* sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. See the Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

However, in the instant case Applicant has provided neither a representative number of species, nor any relevant identifying characteristics of the molecules involved. Instead, claim 1 continues to claim the molecule *only in terms of its function as a CD28 agonist*.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is again invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

7. In view of the comments of record acknowledging that there is enabled subject matter encompassed within the scope of the instant claims; the following rejection under 35 USC 103(a) is set forth with respect to the enabled embodiment of a method of preventing diabetes by administering an anti-CD28 agonist monoclonal antibody to a pre-diabetic subject identified as susceptible to developing diabetes.

Art Unit: 1644

8. Claims 1-6 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabinovitch (Diabetes 43:613-621 1994, IDS-AH) and Lenschow et al. (Immunity 5:285-293 Sept. 1996, IDS-Y), in view of *either* King et al. (Eur. J. Immunol. 25:587-595 1995, IDS-W), *or* Webb et al. (Blood 86:3479-3486 1995, IDS-AQ).

Applicant's argument's, filed 6/5/02, have been fully considered but have not been found convincing.

The claims are drawn to a method of preventing diabetes by administering an anti-CD28 agonist monoclonal antibody to a pre-diabetic subject identified as susceptible to developing diabetes t .

As previously noted, Rabinovitch teaches that multiple immunostimulatory procedures prevent IDDM (autoimmune diabetes) in the NOD mouse (see entire document, e.g., "Title"). Rabinovitch also teaches that the immunostimulation protects from diabetes by favoring T cell differentiation along a protective TH2 pathway, thus downregulating the destructive TH1 response (e.g. page 616-619 "Immunostimulatory Procedures Prevent IDDM: Correction of a Cytokine Balance?", especially page 618-619 bridging paragraph). Rabinovitch concludes that the findings in the NOD mouse provide a basis for considering immunostimulation in attempts to prevent IDDM (autoimmune diabetes) in humans at risk for this disease (e.g., concluding paragraph page 619).

Applicant argues that Rabinovitch teach only that general immune stimulation is useful as a treatment of autoimmune diabetes, and that Rabinovitch fails to teach a method of specifically up-regulating the TH2 arm of the immune response.

The Examiner first notes that Applicant is arguing against the reference individually, and points out that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, as noted previously and reiterated supra, Rabinovitch does teach that the immunostimulation protects from diabetes *by favoring T cell differentiation along a protective TH2 pathway*, thus downregulating the destructive TH1 response (e.g. page 616-619 "Immunostimulatory Procedures Prevent IDDM: Correction of a Cytokine Balance?", especially page 618-619 bridging paragraph). Thus contrary to Applicant's assertion, Rabinovitch does teach a method of specifically up-regulating the TH2 arm of the immune response and clearly appreciates the beneficial effect obtained.

Lenschow et al. teach that the absence of signaling through CD28 in the NOD mouse leads to an accelerated development of diabetes due to the development of a dominant TH1 response (e.g., "Discussion" page 290, especially end of 1st full paragraph). Lenschow et al. further teach that the increased incidence of diabetes occurs when signaling through CD28 is blocked during the first two weeks of life (e.g., page 290, 2nd column, bottom ¼ of text).

Further, Lenschow et al. conclude that it is a disruption of CD28 *signaling* from birth that exacerbates diabetes (e.g., page 289, last full sentence of 1st column). Lenschow et al. also note that disruption of CD28 signaling resulted in a decreased ability to mount a TH2 response (e.g., page 290 1st full paragraph). Throughout the Discussion on pages 290-291, Lenschow et al. clearly teach that it is the inhibition of CD28 signaling during the first two weeks of life that exacerbates disease, thus this teaching would suggest to one of ordinary skill in the art at the time the invention was made that the opposite method of stimulating CD28 signaling during this critical window would have the opposite effect of inducing a TH2 response and protecting from development of diabetes.

Art Unit: 1644

Applicant's comments regarding the mention by Lenschow et al. on page 285, 2nd column, 1st full sentence that their previous studies had shown that blocking B7-2 function (with an anti-B7-2 antibody) also prevented onset of diabetes are acknowledged. Applicant concludes from this comment by Lenschow et al. that one of ordinary skill would expect that upregulating B7-2 binding with CD28 (i.e., agonizing CD28) would induce onset of diabetes.

However, as discussed supra, the teachings of Lenschow et al., when considered in their entirety, address this seeming inconsistent finding and conclude that timing of the signal mediated by CD28 is critical (see entire document, but see especially comments at page 291, 1st column, concluding paragraph).

Applicant's comments regarding the use of NOD mice genetically deficient for the CD28 gene are also acknowledged. Applicant contends that CD28 deficient NOD mice are unrepresentative of the autoimmune diabetes process which is art recognized to occur in NOD mice.

The Examiner acknowledges that CD28 deficient NOD mice differ in their cytokine profiles versus NOD mice expressing CD28. However, these effects are consistent with the role of CD28 in TH2 cell differentiation, and the observed effects are considered by Lenschow et al. Thus the ordinary artisan would take the teachings of Lenschow et al. for all they provide and conclude that since eliminating CD28 signaling from birth accelerates diabetes development, the opposite method of stimulating CD28 signaling during this critical window would have the opposite effect.

Applicant is reminded that obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). MPEP 2143.02.

Neither Rabinovitch nor Lenschow et al. teach a method of preventing diabetes by administering an anti-CD28 agonist monoclonal antibody to a pre-diabetic subject identified as susceptible to developing diabetes

Both King et al. and Webb et al. teach that a CD28 agonist monoclonal antibody induces a TH2 response (see entire document of each, especially "Abstract" and "Methods").

Applicant again argues that the *in vitro* studies of King et al. and Webb et al. do not provide a reasonable expectation that similar results would be obtained *in vivo*. Applicant points to studies of IL-12 receptor blockade and PDE-4 inhibitors for support for this statement.

With regards to the expectation that the antibody employed *in vitro* would not function similarly *in vivo*, the Examiner acknowledges that there can be discrepancies between *in vitro* and *in vivo* results. However, Applicant's arguments rely on unrelated agents then generalizes from these results to address the *in vitro* versus *in vivo* function of a particular agent - anti-CD28 antibodies. Applicant's arguments do not provide objective evidence that these agonistic anti-CD28 antibodies would not have the same effect on T helper cell differentiation to TH2 cells *in vivo* as *in vitro*. Thus Applicant's arguments fail to establish that the ordinary artisan would not reasonably expect anti-CD28 antibodies to function *in vivo* as they do *in vitro*. It is again noted that obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). MPEP 2143.02.

Applicant also points out that King et al. and Webb et al. utilize normal and naive T cells, whereas the T cells targeted in the instant method would be autoimmune.

Art Unit: 1644

Contrary to Applicant's assertions, given the timing of administration that is required for the method to be enabled (i.e., pre-diabetic); the T cells of the instant method would not yet be autoimmune. Therefore, there does not appear to be an clear difference in the cellular populations of the instant method and those of King et al. or Webb et al.

Given the teachings of the references, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an agonistic anti-CD28 antibody in a method for preventing the development of autoimmune diabetes in a pre-diabetic subject susceptible to the development of diabetes. The ordinary artisan at the time the invention was made would have been motivated to administer an agonistic anti-CD28 antibody, such as those taught by King et al. or Webb et al., with the expectation of stimulating the development of a TH2 response, and thus preventing the development of diabetes in a pre-diabetic subject susceptible to developing diabetes, as taught by both Rabinovitch and Lenschow et al. The teachings of both King et al. and Webb et al. show that the ordinary artisan at the time the invention was made would have recognized that an antibody could be used to stimulate CD28, and further that this stimulation results in the TH2 type of response that both Rabinovitch and Lenschow et al. teach protects pre-diabetic susceptible subjects, including human subjects, from diabetes. Consequently, the ordinary artisan would have had a reasonable expectation of success in preventing development of diabetes in pre-diabetic subjects susceptible to the development of diabetes, including in humans. In view of the teachings of Lenschow et al. that the critical window is in the first two weeks of life in the murine model, the ordinary artisan would have been further motivated to select pre-diabetic human subjects identified as susceptible to the development of diabetes for therapy in the corresponding period of life, i.e., at from about 6 months to about 2-3 years. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
August 26, 2002

Phillip P. Gambel
PHILLIP GAMBEL, PH.D.
PRIMARY EXAMINER
TECH CENTER 1600
8/26/02